

16. A method of treating epilepsy in a mammal comprising the step of administering to said mammal a therapeutically effective amount of a composition as defined in claim 1.

17. A method of treating a neurological condition in a mammal comprising the step of administering to said mammal a therapeutically effective amount of a composition as defined in claim 1.

A3
cont.
18. A method of treating a neurodegenerative disease in a mammal comprising the step of administering to said mammal a therapeutically effective amount of a composition as defined in claim 1.

19. A method of repairing a nervous system injury in a mammal comprising the step of administering to said mammal a therapeutically effective amount of a composition as defined in claim 1.

REMARKS

Reconsideration and allowance of the subject application are respectfully requested.

Claims 1-4 has been amended to clarify the definition of R^1 , R^2 and R^3 . Claims 5-7 and 13 have been amended to reduce the number of recited compounds. Claims 14-19 have been added and are supported in the present application at page 2, lines 12-29 and page 14, lines 6-15. In

summary, it is believed that no new subject matter has been added to the present application by the amendments presented herein.

Accordingly Claims 1-7 and 9-19 currently stand in the present application. Claims 1 and 13 are independent.

In Paragraph 2 of Paper Number 5, the Examiner rejected Claims 1-12 under 35 U.S.C. §112 (second paragraph) as purportedly being indefinite. This rejection is traversed. Reconsideration is requested in light of the amendments submitted herewith and the following remarks.

The Examiner's suggestion in Paragraph 2(a) of Paper Number 5 has been adopted.

The rejection in Paragraph 2(b) of Paper Number 5 should have been applied to Claim 5. Notwithstanding this, the rejection is moot since this compound is not referred to in Claim 5, as amended herein.

The rejection in Paragraph 2(c) of Paper Number 5 is moot since the latter compound is not referred to in any of Claims 5-7 and 13, as amended herein (Claim 8 has been cancelled without prejudice or disclaimer).

The rejection in Paragraph 2(d) of Paper Number 5 is traversed. The specification, in the hands of a person of ordinary skill in the art, provides a clear description of "neurotrophin-mediated activity". See, for example, the present application at: page 1, line 20 to

page 2, line 29; page 13, line 20 to page 14, line 5. Notwithstanding this, the term "neurotrophin-mediated activity" is discussed clearly in the present application on page 5, line 26 to page 6, line 8.

In summary, the Examiner is requested to reconsider and withdraw the rejection of Claims 1-12 under 35 U.S.C. §112 (second paragraph).

The Examiner raises a number of prior art rejections in Paper Number 5. Most of these rejections were raised under 35 U.S.C. §102(b). All prior art rejections are traversed.

The Examiner is requested to reconsider and withdraw all rejections under 35 U.S.C. §102(b) in light of the following remarks.

Regarding the rejection of Claims 1-3 and 9 as being purportedly anticipated by Costi (Paragraph 4 of Paper Number 5) and Claims 1-4 and 9-12 as being purportedly anticipated by Malizia or Semenovich (Paragraph 6 of Paper Number 5), Applicant wishes to point out that Claim 1 of the present application has been amended herein to recite that R^2 and R^3 cannot both be hydrogen. As such, these Claims are not anticipated by Costi or Malizia. This is also a feature of independent Claim 13 of the present application, as amended herein. Accordingly, Applicant submits that none of Costi, Malazia or Semenovich anticipates the Claims of the present application, as amended herein.

Regarding the rejection of old Claims 1-12 as being purportedly anticipated by either Sestanj I (Paragraph 5 of Paper Number 5) or Sestanj II (Paragraph 7 of Paper Number 5), Applicant notes that the moiety R^1 of the compound of Formula I in Claim 1, as amended herein,

does not read on to the moieties taught at this position in either of the prior art references. This distinction is also found in independent Claim 13 of the present application, as amended herein. Accordingly, Applicant submits that neither Sestanj I nor Sestanj II anticipates the Claims of the present application, as amended herein.

Regarding the rejection of old Claims 1-3 and 9 as being purportedly anticipated by Brana I (Paragraph 8 of Paper Number 5) and Claims 1-9 and 13 as being purportedly anticipated by Brana II, Applicant notes that, for these references to be applicable, R¹ in the compound of Formula I in Claim 1 of the present application would have to read on to the moiety -CH₂COOH. As the Examiner will note, R¹ in the compound of Formula I of the present application (as amended herein) does not read on such a moiety. This distinction is also found in independent Claim 13. Accordingly, Applicant submits that neither Brana I nor Brana II anticipates the Claims of the present application, as amended herein.

In light of the foregoing comments, Applicant submits Claims 1-13 distinguish over the prior art relied on by the Examiner in raising the various rejections under 35 U.S.C. §102(b). Accordingly, the Examiner is requested to reconsider and withdraw all rejections based on 35 U.S.C. §102(b).

The Examiner rejected old Claim 13 under 35 U.S.C. §103(a) as being purportedly unpatentable over Sestanj I in view of Bundgaard. This rejection is traversed. Reconsideration is requested in view of the following remarks.

The Examiner relies on Sestanj I for the teaching of a specific compound which is not covered by any Claim in the present application, as amended herein. The Examiner relies on Bundgaard for the production of an ester or amide analogue as a prodrug of the compound taught by Sestanj. As stated above, Sestanj fails to teach a compound covered by any claim in the present application. Thus, modifying its teachings as proposed by the Examiner does not alleviate the shortcomings of the Sestanj reference. Sestanj simply fails to teach or suggest any compound covered by the claims of the present application. Accordingly, the Examiner is requested to reconsider and withdraw the rejection.

The Examiner rejected old claims 1-3 and 9 under 35 U.S.C. §103(a) as being purportedly unpatentable in view of Brana III. This rejection is traversed. Reconsideration is requested in light of the following remarks. The Examiner relies on Brana III for the teaching of a bisnaphthalimide having cytotoxic activity. As the Examiner will note, since the claims of this present application no longer include such compounds, it is believed that this rejection is now moot. The Examiner is requested to reconsider and withdraw the rejection in view of Brana III.

In Paragraphs 13 and 14 of Paper Number 5, the Examiner raises a provisional obviousness-type double patenting rejection against Claims 1-13 in view of copending application S.N. 09/457,606. To substantiate the provisional rejection, the Examiner states: "Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are encompassed by the copending claims." The provisional rejection is traversed and reconsideration is requested in light of the following remarks. Applicant submits that the

amendments made to the Claims of the present application and amendments made to the Claims of the '606 application have resulted in there being no overlap between the Claims of the respective applications. Accordingly, the Examiner is requested to reconsider and withdraw the provisional rejection.

In light of the foregoing, the Examiner is requested to reconsider and withdraw all prior art rejections.

In view of the above amendments and remarks, it is believed that this application is now in condition for allowance, and a Notice thereof is respectfully requested.

Applicants' undersigned agent may be reached by telephone at (416) 862-5775.

All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

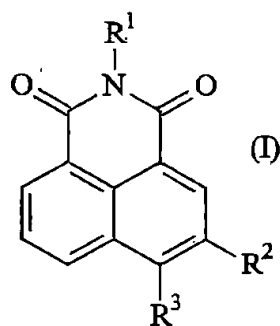


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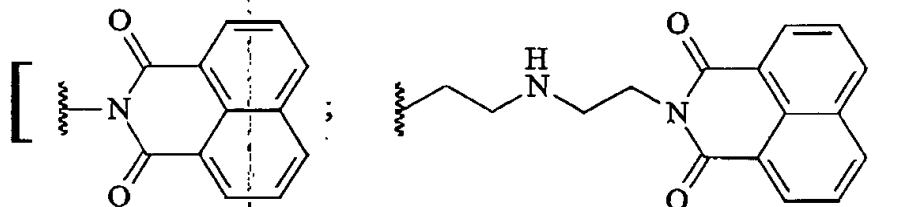
Marked-up Claims

1. A pharmaceutical composition comprising a compound of Formula I,

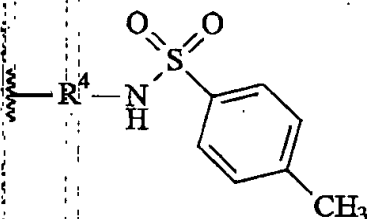


wherein

R¹ is selected from alkyl; aryl-loweralkyl; [heterocycle-loweralkyl;] loweralkyl-carbonate; amino [optionally] monosubstituted or disubstituted with a [substituent selected from loweralkyl, aryl and] hydroxyloweralkyl; benzimidaz-2-yl;



and]

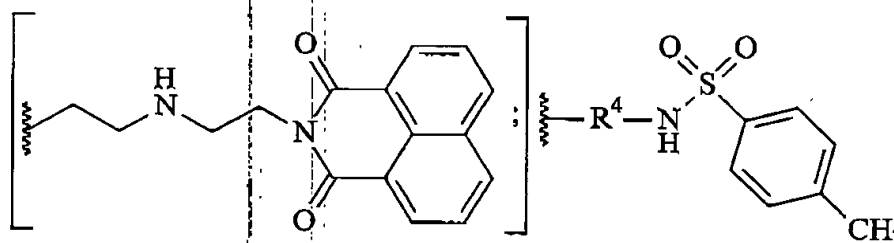


wherein R^4 is phenyl optionally monosubstituted or disubstituted with a substituent selected from loweralkyl and halo; phenyl optionally monosubstituted or disubstituted with a substituent selected from amino, loweralkoxy, hydroxy and loweralkyl; $NHCH_2CH_2OX$ wherein X represents an *in vivo* hydrolyzable ester; and [loweralkyl] C_2-C_4 alkyl- $(R^5)(R^6)$ wherein one of R^5 and R^6 is selected from H and loweralkyl and the other is selected from carboxy, carboxy-loweralkyl and loweralkoxycarbonyl; and

R^2 and R^3 are independently selected from H, NO_2 , halo, di(loweralkyl)amino, cyano, $C(O)OH$, phenyl-S-, loweralkyl, and $Z(O)OR^7$ wherein Z is selected from C and S and R^7 is selected from H, loweralkylamino and arylamino, with the proviso that both R^2 and R^3 are not both hydrogen;

and pharmaceutically acceptable salts thereof, in an amount effective to inhibit neurotrophin-mediated activity, and a [suitable] pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to claim 1, wherein R^1 is selected from alkyl; aryl-loweralkyl; [heterocycle-loweralkyl;] loweralkyl-carbonate; amino [optionally] monosubstituted or disubstituted with a [substituent selected from loweralkyl and] hydroxyloweralkyl; benzimidaz-2-yl;



wherein R^4 is phenyl optionally monosubstituted or disubstituted with a substituent selected from loweralkyl and halo; phenyl optionally monosubstituted or disubstituted with a substituent selected from amino, loweralkoxy, hydroxy and loweralkyl; $NHCH_2CH_2OX$ wherein X represents an *in vivo* hydrolyzable ester; and [loweralkyl] C_2-C_4 alkyl- $(R^5)(R^6)$ wherein one of R^5 and R^6 is selected from H and loweralkyl and the other is selected from carboxy, carboxy-loweralkyl and loweralkoxy-carbonyl; and

R^2 and R^3 are independently selected from H, NO_2 , halo, di(loweralkyl)amino, loweralkyl and phenyl-S-, with the proviso that both R^2 and R^3 are not both hydrogen.

3. A pharmaceutical composition according to claim 2, wherein R^1 is selected from aryl-loweralkyl; [heterocycle-loweralkyl]; loweralkyl-carbonate; amino [optionally] monosubstituted or [disubstituted] disubstituted with [a substituent selected from loweralkyl and] hydroxyloweralkyl; benzimidaz-2-yl; $NHCH_2CH_2OX$ wherein X represents an *in vivo* hydrolyzable ester; and [loweralkyl] C_2-C_4 alkyl- $(R^5)(R^6)$ wherein one of R^5 and R^6 is selected from H and loweralkyl and the other is selected from carboxy, carboxy-loweralkyl and loweralkoxy-carbonyl; and

R^2 and R^3 are independently selected from H, NO_2 , di(loweralkyl)amino, loweralkyl and phenyl- S_{-2} , with the proviso that both R^2 and R^3 are not both hydrogen.

4. A pharmaceutical composition according to claim 3, wherein R^1 is selected from amino [optionally] monosubstituted or [disubstituted] disubstituted with [a substituent selected from loweralkyl and] hydroxyloweralkyl; $NHCH_2CH_2OX$ wherein X represents an *in vivo* hydrolyzable ester; and [loweralkyl] C_2-C_4 alkyl- $(R^5)(R^6)$ wherein one of R^5 and R^6 is selected from H and loweralkyl and the other is selected from carboxy, carboxy-loweralkyl and loweralkoxy-carbonyl; and

R^2 and R^3 are independently selected from H, loweralkyl and NO_2 , with the proviso that both R^2 and R^3 are not both hydrogen.

5. A pharmaceutical composition according to claim 1 wherein the compound of Formula I is selected from the group consisting of:

N-{5-Nitro-1H-benz[de]isoquinoline-1,3(2H)-dione}-2-aminoethanol;

[N-Dimethylamino-1,3-dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline;
N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)acetic acid;
N-Acetoxy-1,3-dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline;
N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)aminoethanol;
N-Furfuryl-1,8-naphthalimide;
6-(N,N-Dimethylamino)-2-(benzimidazol-2-yl)naphthalimide;
N-(Pyrid-2-ylethyl)-1,8-naphthalimide;
1,3-Dioxo-6-phenylmercapto-N-(pyrid-2-ylethyl)-1,2,3,4-tetrahydro-
benzo[i]isoquinoline;]
2-{2-(4-Methylphenylsulphonamido)phenyl}-6-(N,N-dimethylamino)-
naphthalimide;
[1,3-Dioxo-2-{2-(4-methylphenylsulphonamido)phenyl}-1,2,3,4-tetrahydro-
benzo[i]isoquinoline;]
N-Octyl-5-nitronaphthalimide;
[5-Bromo-1,3-dioxo-N-methylpyrid-3-yl-1,2,3,4-tetrahydrobenzo-
[i]isoquinoline;
1,3-Dioxo-5-nitro-N-(pyrid-2-ylethyl)-1,2,3,4-tetrahydro[i]isoquinoline;
6-Nitro-2-(tetrahydrofuran-2-ylmethyl)naphthalimide;
N-(1,3-Dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline)aminoethanol;
Naphthalicacid-N-aminoimide;]
2-{2-(4-Methylbenzsulphonamido)-4,5-dichlorophenyl}naphthalimide;

3-Nitro-1,8-(N-propioncarboxylate)succinamidonaphthalene;
[1,3-Dioxo-2-(2-aminophenyl)-1,2,3,4-tetrahydrobenzo[i]isoquinoline;
6-Nitro-2-(pyrid-3-methyl)naphthalimide;]
3-Amino-7,4-bis(ethyl-1,3-dioxo)-1,2,3,4-tetrahydrobenzo[i]isoquinoline;
2-(Benzimidaz-2-yl)-1,3-dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline;
[2-(2-Aminophenyl)naphthalimide;]
1,3-Dioxo-2-{4,5-dimethyl-2-(4-methylphenylsulphonamido)phenyl}-
1,2,3,4-tetrahydrobenzo[i]isoquinoline;
3-Methyl-3-(1,3-dioxo-5-nitro(1H,3H)benz[de]isoquinolyl)butyric acid methylester;
[1,3-Dioxo-N-methyltetrahydrofurfur-2-yl-5-nitro-1,2,3,4-tetrahydro-
[i]isoquinoline;]
N-(4-Ethoxyphenyl)-5-nitronaphthalimide;
[6-Nitro-2-(furfuryl)naphthalimide;]
Ethyl-5-nitro-1,3-dioxo-1H-benz[de]isoquinoline-2-3H-acetate;
Naphthalicacid-N,N'-diimide;
[2-(2-Hydroxyphenyl)naphthalimide;]
5-Amino-N-butyl naphthalimide;
1,3-Dioxo-5-nitro-n-propylmorpholino-1,2,3,4-tetrahydrobenzo[i]isoquinoline; and
[6-Nitro-2-(pyrid-2-ylethyl)naphthalimide;
N-Methylnaphthalimide;
N-(Pyrid-2-ylmethyl)naphthalimide;

N-(3,5-Dimethylphenyl)-1,8-naphthalimide;

6-Bromo-N-dimethylamino-1,3-dioxo-1,2,3,4-tetrahydrobenzo-
[i]isoquinoline;

N-(1,3-Dioxo-6-phenylmercapto-1,2,3,4-tetrahydrobenzo[i]isoquinoline)-
aminoethanol[; and

N-Anilino-1,8-naphthalimide].

6. A pharmaceutical composition according to claim 2 wherein the compound of Formula I is selected from the group consisting of:

N-{5-Nitro-1H-benz[de]isoquinoline-1,3(2H)-dione}-2-aminoethanol;

[N-Dimethylamino-1,3-dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline;

N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)acetic acid;

N-Acetoxy-1,3-dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline;

N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)aminoethanol;

N-Furfuryl-1,8-naphthalimide;

6-(N,N-Dimethylamino)-2-(benzimidazol-2-yl)naphthalimide;

N-(Pyrid-2-ylethyl)-1,8-naphthalimide;

1,3-Dioxo-6-phenylmercapto-N-(pyrid-2-ylethyl)-1,2,3,4-tetrahydro-
benzo[i]isoquinoline;

2-{2-(4-methylphenylsulphonamido)phenyl}-6-(N,N-dimethylamino)-
naphthalimide;

1,3-Dioxo-2-{2-(4-methylphenylsulphonamido)phenyl}-1,2,3,4-tetrahydro-
benzo[i]isoquinoline;]

N-Octyl-5-nitronaphthalimide;

[5-Bromo-1,3-dioxo-N-methylpyrid-3-yl-1,2,3,4-tetrahydrobenzo-
[i]isoquinoline;

1,3-Dioxo-5-nitro-N-(pyrid-2-ylethyl)-1,2,3,4-tetrahydro[i]isoquinoline;

6-Nitro-2-(tetrahydrofuran-2-ylmethyl)naphthalimide;

N-(1,3-Dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline)aminoethanol;

Naphthalicacid-N-aminoimide;]

2-{2-(4-Methylbenzsulphonamido)-4,5-dichlorophenyl}naphthalimide;

3-Nitro-1,8-(N-propioncarboxylate)succinamidonaphthalene;

[1,3-Dioxo-2-(2-aminophenyl)-1,2,3,4-tetrahydrobenzo[i]isoquinoline;

6-Nitro-2-(pyrid-3-methyl)naphthalimide;]

3-Amino-7,4-bis(ethyl-1,3-dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline; and

2-(Benzimidaz-2-yl)-1,3-dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline[; and

2-(2-Aminophenyl)naphthalimide].

7. A pharmaceutical composition according to claim 3 wherein the compound of Formula I is
[selected from the group consisting of:]

N-{5-Nitro-1H-benz[de]isoquinoline-1,3(2H)-dione}-2-aminoethanol[;

N-Dimethylamino-1,3-dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline;

N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)acetic acid;
 N-Acetoxy-1,3-dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline;
 N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)aminoethanol;
 N-Furfuryl-1,8-naphthalimide;
 6-(N,N-Dimethylamino)-2-(benzimidazol-2-yl)naphthalimide;
 N-(Pyrid-2-ylethyl)-1,8-naphthalimide; and
 1,3-Dioxo-6-phenylmercapto-N-(pyrid-2-ylethyl)-1,2,3,4-tetrahydro-
 benzo[i]isoquinoline] or its pharmaceutically acceptable salt.

13. An *in vivo* hydrolyzable ester or amide of a compound selected from the group consisting of:

N-{5-Nitro-1H-benz[de]isoquinoline-1,3(2H)-dione}-2-aminoethanol;
 [N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)acetic acid;
 N-(1,3-Dioxo-5-nitro-1,2,3,4-tetrahydrobenzo[i]isoquinoline)aminoethanol;
 N-(1,3-Dioxo-1,2,3,4-tetrahydrobenzo[i]isoquinoline)aminoethanol;
 Naphthalicacid-N-aminoimide;]
 3-Nitro-1,8-(N-propioncarboxylate)succinamidonaphthalene;
 [1,3-Dioxo-2-(2-aminophenyl)-1,2,3,4-tetrahydrobenzo[i]isoquinoline;]
 3-Amino-7,4-bis(ethyl-1,3-dioxo)-1,2,3,4-tetrahydrobenzo[i]isoquinoline; and
 [2-(2-Aminophenyl)naphthalimide; and]
 2-(2-Hydroxyphenyl)naphthalimide.